REMARKS

In view of the foregoing amendments and the following representations, reconsideration and allowance of the above-identified application is respectfully requested.

Claims 12-27 are in the present application and pending.

In the Office Action on page 2, paragraph 2, the Examiner objected to the specification because it did not provide support for the phrase "co-polymerized methacrylic acid/methacrylic acid methyl esters" as recited in original claim 4 and currently pending claims 16 and 24. In response to this objection, Applicants have amended page 4 of the specification to include the phrase "co-polymerized methacrylic acid/methacrylic acid methyl esters". No new matter is added by this amendment. Support can be found in claim 4 as originally filed.

On page 2, paragraph 3 of the Office Action, the Examiner objected to claims 12-27 because of the transition phrase "consists essentially of". In response to this objection, Applicants have amended claims 12-14, 18-22 and 26-27 by deleting the phrase "consists essentially of" and replacing it with "consisting essentially of". No new matter is added by these amendments.

On pages 2-4 of the Office Action, the Examiner rejected claims 12-27 under the judicially created doctrine of obviousness type double patenting in view of United States Patent No. 6,733,778. The Examiner also indicated that the same rejection could be

made for United States Patent Nos. 6,602,522, 6,174,548 and 6,096,340 and requested that the Applicants review the files and submit the appropriate terminal disclaimers.

As suggested by the Examiner, Applicants have reviewed the files for patents and applications relating to omeprazole formulations. Based upon this review Applicants have identified two series of patents and applications. The first series comprises United States Patent Nos. 6,096,340; 6,077,541 and 6,780,435 which all claim priority to United States Patent Application Serial No. 08/970,489 filed on November 14, 1997, are assigned to Andrx Pharmaceuticals, Inc. of Fort Lauderdale, Fla. This first series lists Chih-Ming Chen, Joseph C.H. Chou and Timothy Weng as inventors. The second series includes the present application, United States Patent Nos. 6,174,548 and 6,733,778 and allowed United States Patent Application Serial No. 10/712,505 filed on November 13, 20003. The second series all claim priority to United States Patent Application Serial No. 09/143,167 filed on August 28, 1998, are assigned to Andrx Pharmaceuticals, Inc. of Fort Lauderdale, Fla. and list Chih-Ming Chen, Joseph Chou and Unchalee Kositprapa as the inventors.

Applicants will file terminal disclaimers for all the patents and allowed applications identified in the preceding paragraph upon the finding of allowable subject matter. It is respectfully submitted that the filing of the terminal disclaimers upon the finding of allowable subject matter will obviate the rejection of the pending claims based upon obvious type double patenting.

On page 5 of the Office Action, the Examiner rejected claims 12-27 under 35 U.S.C. § 103(a) as being obvious over Chen et al., United States Patent No. 6,780,435, in view of Lundberg et al. U.S. 6,013,281. On page 7 of the Office Action the Examiner rejected claims 12-27 under 35 U.S.C. § 103(a) as being unpatentable over Lundberg et al., United States Patent No. 6,013,281.

The Examiner indicated that the Chen reference was prior art under 35 U.S.C. § 102(e) only and suggested a number of ways the rejection might be overcome. In accordance with the Examiner's helpful suggestions, it is respectfully submitted that the current application and the Chen reference are owned by the same entity, Andrx Pharmaceuticals, Inc. It is also respectfully submitted that the current application and the Chen reference share two common inventors, i.e. Chih-Ming Chen and Joseph Chou. A declaration in accordance with the provisions of 37 C.F.R. § 1.130 is attached hereto as Exhibit A that verifies these facts. In view of the attached declaration and the commitment to file a terminal disclaimer upon the finding of allowable subject matter as stated above, it is respectfully submitted that rejection of the pending claims based upon the Chen reference has been overcome.

It is also submitted that the pending claims are patentable over the Lundberg reference. The pending claims recite a stable enteric coated omeprazole pellet that consists essentially of a core onto which an enteric coating is directly applied without the need of applying a separate sublayer. More importantly, the pending claims also require that the core contain 0.5 to 10% based upon the total weight of the core of arginine

or lysine and that the enteric coating contain 5-50 weight percent of an inert processing aid based upon the weight of the enteric coating. As explained in detail during the prosecution of the parent application, United States Patent No. 6,733, 778, this unique combination of a low amount of arginine or lysine in the core of an omeprazole pellet and high amount of inert processing aid in the enteric coating of an omeprazole pellet without the application of a separating layer is not disclosed or suggested by any of the numerous prior art references of record.

Applicants agree with the Examiner that the Lundberg reference discloses the use of arginine and lysine as alkaline agents on Col. 6, lines 50-55, however, these compounds are only two of the many alkaline agents listed in the cited section of the Lundberg reference. More importantly, the next few paragraphs, Col. 7, lines 6-26, suggest that a large amount, i.e. 85% of the core weight, of an alkaline agent may be required. Further, Example 1 is only one example in the Lundberg reference that describes an omeprazole pellet which employs arginine or lysine. This example employs approximately 69% by weight of the core of arginine[1].

Therefore based upon the teachings of the Lundberg reference, an individual of ordinary skill in the art would be lead to use large amounts of arginine or lysine in the core of an omeprazole pellet and not the small amounts recited in the pending claims.

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[1] Example 6 employs omeprazole and arginine but Example 6 is a tablet, not a pellet, as recited in the pending claims. The chemical and physical properties of a tablet and pellet are different due at least to methods of manufacture and differences in surface area.

In the paragraph bridging pages 8 and 9 of the Office Action, the Examiner indicated that amounts of the inert processing aid in the enteric coating will not support patentability absence evidence that the concentration is critical. In response to this comment by the Examiner, Applicants submit Exhibit B, which is an article entitled "Effects of Solids – Polymer Interactions on the Properties of Some Aqueous – Based Tablet Film Coating Formulations" by Okhamafe et al., International Journal of Pharmaceutics, 22 (1984) 265-272. This article describes a number of experiments on hydroxypropyl methylcellulose films with varying amounts of talc. Although this article does not contain experiments on enteric coatings as recited in the pending claims, it does teach that "the fundamental properties of coatings are likely to be affected to varying degrees when fillers are incorporated". p. 266. The article also states the effect of particulate solids on film properties depends on a variety of factors and therefore "[i]t is difficult to determine precisely the contribution of each of these factors to any particular film property." P. 266. The teachings of this article confirm that it is difficult, if not impossible, to determine the effects an inert filler will have on a pharmaceutical film.

It is respectfully submitted that based upon the general knowledge in the pharmaceutical arts as evidenced by Exhibit B, that the amount of inert filler recited in the claims is critical. Moreover, it is the unique combination of the amount of inert filler in the enteric coating and the amount of arginine or lysine in the core of the pellet that allows Applicants to obtain a stable omeprazole pellet without the need to apply a separating

layer between the core and the enteric coating as taught by the numerous prior art references of record.

To further support the unique and patentable nature of the omeprazole pellet formulation recited in the pending claims, Applicants wish to remind the Examiner of the well known problems in preparing omeprazole pellet formulations which are stated in United States Patent No. 4,786,505 as follows:

> In order to obtain a pharmaceutical dosage form of omeprazole which prevents omeprazole from contact with acidic gastric juices, the cores must be enteric coated. Ordinary enteric coatings, however, are made of acidic compounds. If covered with such a conventional enteric coating, omeprazole rapidly decomposes by direct or indirect contact with it, with the result that the preparations become badly discolored and lose in omeprazole content with the passage of time.
>
> In order to enhance the storage stability the cores which contain omeprazole must also contain alkaline reacting constituents. When such an alkaline core is enteric coated with an amount of a conventional enteric coating polymer such as, for example, cellulose acetate phthalate, that permits the dissolution of the coating and the active drug contained in the cores in the proximal part of the small intestine, it also will allow some diffusion of water of gastric juice through the enteric coating into the cores, during the time the dosage form resides in the stomach before it is emptied into the small intestine. The diffused water of gastric juice will dissolve parts of the core in the close proximity of the enteric coating layer and there form an alkaline solution inside the coated dosage form. The alkaline solution will interfere with the enteric coating and eventually dissolve it...
>
> If a conventional formulation of omeprazole is made the stability is not satisfactory, particularly in resistance to humidity, and special moisture-proof packing has been adopted to minimize the troubles. However, this provides no satisfactory solution to the problems in today's drug distribution systems and also leads to increased costs.

Col. 1, line 48 to Col. 2, line 23 of United States Patent No. 4,786,505 (See also Table 3 and Comparative Examples I-V which show that non-subcoated omeprazole pellets are not stable).

The solution to the stability problems proposed by the inventors of United States Patent No. 4,786,505 was to insert a water soluble sublayer between the omeprazole core and the enteric coating. This was generally the accepted technique for preparing stable enteric coated omeprazole pellets until the Lundberg reference. The solution proposed by the Lundberg reference is to provide enough alkaline material in the core to react with the enteric coating to form a separating layer between the omeprazole in the core the enteric coating. With respect to arginine omeprazole pellets, this amount was greater than 50% of arginine in the core of the pellet.

Thus, the Lundberg reference teaches an individual of ordinary skill in the art to use large amounts of arginine in the core of an omeprazole pellet and not the small amounts recited in the pending claims. Further, as evidenced by Exhibit B, the addition of a large amount of inert filler to the enteric coating would probably not be viewed as a potential solution because as Exhibit B suggests as the amount of inert filler in a pharmaceutical coating can adversely affect properties of the coating.

Based upon the foregoing amendments and representations, it is respectfully submitted that the pending claims which require a stable omeprazole pellet with a low amount of arginine or lysine in the core and a high amount of inert filler in the enteric coating are patentable over the cited references. Once the Examiner

indicates that the claims contain allowable subject matter, the terminal disclaimers will be provided. Early and favorable action is earnestly solicited.

Respectfully submitted,

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